November 25, 2024

Department of Health and Human Services (HHS)
Food and Drug Administration (FDA)

RE: Microbiology Devices; Reclassification of Antigen, Antibody, and Nucleic Acid-Based Hepatitis B Virus Assay Devices [Docket No. FDA-2024-N-3533]

Attn:
Maria Ines Garcia, PhD
Assistant Director Virology
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 66, Rm. 3104
Silver Spring, MD 20993

Dear Dr. Garcia,

On behalf of the Hepatitis B Foundation (HBF), Hep B United coalition (HBU), and the 47 undersigned organizations, thank you for the opportunity to provide comments on the reclassification of hepatitis B virus assay devices. The proposed U.S. Federal Drug Administration (FDA) re-classification of hepatitis B diagnostics is an excellent move towards improving access to hepatitis B screening and diagnosis. This action will promote availability of point-of-care (POC) tests, which will increase the number of people with hepatitis B who are diagnosed and can access care and treatment, reducing deaths related to hepatitis B and liver cancer.

The proposed FDA re-classification of hepatitis B diagnostics is a long-awaited move towards improving access to hepatitis B screening and diagnosis, particularly among the communities that are most impacted by hepatitis B in the U.S. (communities of color, foreign-born communities, the LGBTQ community, and people who use drugs)[1,2,3]. These groups face an exceptional set of social determinants that serve as barriers to diagnosis and lead to reduced access to healthcare. It is estimated that only 25%-30% of people living with hepatitis B in the U.S. have been diagnosed[4].

There are no FDA-cleared POC tests available in the U.S., which has contributed to continuing low hepatitis B diagnosis rates. Currently, only laboratory-based hepatitis B diagnostics are available, which require a blood draw. Blood draws are associated with increased cost, can be logistically difficult to perform in low-threshold care settings such as harm reduction programs or community-based care, and there is often fear associated with blood draws, making many hesitant to get screened. Multiple visits are needed, which is a barrier for many, particularly communities with barriers to accessing health services. Additionally, it can take up to a week for test results to be relayed back to the patient, which further increases the number of people lost-to-follow up. This is a particular concern in community screening settings, where a large percentage of high-risk individuals are screened. In many settings, POC rapid diagnostic tests (RDT) have advantages over standard laboratory-based tests, as they can provide reliable results in a timely manner in a setting where the patient can remain engaged in care[5,6].

In light of the recent recommendation by the Centers for Disease Control and Prevention (CDC), the U.S. Department of Health and Human Services' (HHS) target to eliminate viral hepatitis by 2030, the

proposed White House Plan to eliminate hepatitis C, and the prospect of new and potentially more effective therapeutics in the research pipeline, we believe there is now a window of opportunity for the U.S. to achieve its goal of eliminating viral hepatitis by 2030, and reduce the health disparities experienced by those living with hepatitis B. We are also encouraged by the recent request for proposals launched through the National Institutes of Health (NIH) Rapid Acceleration of Diagnostics (RADx) Tech program in collaboration with the FDA, to "accelerate the validation, regulatory authorization, and commercialization of innovative point of care POC tests for hepatitis B virus surface antigen (HBsAg) detection[7]."

The Hepatitis B Foundation applauds the U.S. FDA proposal to reclassify hepatitis B diagnostics, and strongly encourages the following considerations:

- **Setting reasonable cutoff values for test sensitivity and specificity.** This would make it feasible for a POC test to be available in the U.S., especially in community care settings, while limiting false positives and false negatives. We believe that POC tests should have reasonable sensitivity and specificity that are comparable to the current World Health Organization (WHO) pre-qualified tests[8,9]. Additionally, in a possible scenario where a POC HBsAg test has lower sensitivity, we recommend consideration of a statement about reflex testing to the triple panel (HBsAg, HBsAb, HBcAb), as HBsAg negative results could be misleading in this situation.
- **Clarifying re-classification of hepatitis B core antibody tests.** In the draft recommendation, it seems unclear whether both hepatitis B core antibody IgM (HBcAb IgM) and hepatitis B core antibody total (HBcAb total) are included in the proposed re-classification. We urge clarity in the final recommendation.
- **Reliable data obtained from approved hepatitis B POC tests used globally when setting the required sample size within the U.S.** It is important to acknowledge that several hepatitis B POC tests have been designated as "WHO pre-qualified" and/or "CE-marked" and have been used globally for many years.[10]
- **Reclassifying quantitative HBsAg assays**. The future clinical utility of the quantitative hepatitis B surface antigen test is anticipated to be significant. This will be particularly important as quantitative HBsAg is used to monitor response for new therapies currently in phase II and phase III trials. Looking at data from these trials, it is almost certain that quantitative HBsAg will be necessary to predict response and monitor efficacy of these new therapies post-approval[11,12,13].
- **Consider a CLIA-waiver designation for hepatitis B testing for the final rule.** This designation would help in making these tests available in settings where hepatitis B POC testing would be most useful, such as harm reduction programs and other community screenings.

Hepatitis B Foundation is the nation's leading nonprofit research and disease advocacy organization focused on hepatitis B. For the past 33 years, the Foundation's commitment has included funding hepatitis B focused research, promoting disease awareness, supporting screening, vaccination and treatment initiatives, and serving as the primary source of information for patients and families, the medical and scientific community, and the general public. The Foundation co-leads national coalitions (Hep B United, and the Coalition Against Hepatitis for People of Africa Origin) in 40 cities and 27 states, working to eliminate the health disparities associated with hepatitis B, and reaching over 6 million people across the U.S.

Thank you again for the opportunity to provide comments on the proposed reclassification of hepatitis B virus assay devices. Please contact Yasmin Ibrahim, Program Director of Public Health (yasmin.ibrahim@hepb.org) with any questions or to request additional information.

Sincerely,

African Cultural Alliance of North America (ACANA)
American Association for the Study of Liver Diseases
Asian Health Coalition
Asian Pacific American Medical Student Association
Association of Asian Pacific Community Health Organizations
BROWNSVILLE HEALTH AND WELLNESS CENTERS, BROOKLYN, NY
Caring Ambassadors Program
Charles B. Wang Community Health Center, Inc.
Community Liver Alliance
DeLIVER Care Van/UCSF
Empire Liver Foundation
End Hep C SF
EPIH/ SOS HEPATITES RD CONGO
Equality California
Five Horizons Health Services
Global Liver Institute
GSK
Hawai'i Health & Harm Reduction Center
Hep B United
Hep B United Philadelphia
Hep Free Hawai'i
Hepactive Association
Hepatitis Advocacy Foundation (HAF)
Hepatitis B Foundation
Hepatitis B and Hepatitis Delta Global Community Action Board
HepBCommunity.org
HIV Medicine Association
HIV+Hepatitis Policy Institute
Illinois Public Health Association
International Network on Health and Hepatitis in Substance Users (INHSU)
Korean Community Services
NASTAD
National Task Force on Hepatitis B
National Viral Hepatitis Roundtable (NVHR)
National Working Positive Coalition
New York City Department of Health and Mental Hygiene
Patients with Hepatitis, Albania
Sierra Leone Nurses Association
Society on Liver Disease in Africa (SOLDA)
The AIDS Institute
The National Organisation for People Living with Hepatitis B
Treatment Action Group
United Liver Arizona & New Mexico
VEN Centers
Vivent Health
World Hepatitis Alliance

Yellow Warriors Society Philippines

(1) Williams DR, Rucker TD. Understanding and addressing racial disparities in health care. *Health Care Financ Rev*. 2000;21(4):75-90.
(2) Lim JK, Nguygen MH, Kim WR, Gish R, Perumalswami P, et al. (2020) Prevalence of chronic hepatitis B virus infection in the United States. *Am J Gastroenterol* 115: 1429-1438.
(3) Wong RJ, Brosgart CL, Welch S, Block T, Chen M, et al. (2021) An updated assessment of chronic hepatitis B prevalence among foreign-born persons living in the United States. *AASLD Hepatology* 74: 607-626.
(4) Kim HS, Rotundo L, Yang JD, Kim D, Kothari N, Feurdean M, et al. Racial/ethnic disparities in the prevalence and awareness of Hepatitis B virus infection and immunity in the United States. J Viral Hepat. 2017;24:1052-1066.
(5) Khuroo MS, Khuroo NS, Khuroo MS. Accuracy of Rapid Point-of-Care Diagnostic Tests for Hepatitis B Surface Antigen-A Systematic Review and Meta-analysis. J Clin Exp Hepatol. 2014 Sep;4(3):226-40. doi: 10.1016/j.jceh.2014.07.008. Epub 2014 Aug 28.
(6) Ana Avellon, Aftab Ala, Antonio Diaz, Daniel Domingo, Rosario Gonzalez, Lorena Hidalgo, Paul Kooner, Sabarinathan Loganathan, Dolores Martin, Stuart McPherson, et al. Clinical performance of Determine HBsAg 2 rapid test for Hepatitis B detection. Journal of Medical Virology 2020; 92(12): 3403-3411 https://doi.org/10.1002/jmv.25862
(7) Cimit. RADx® Tech Independent Test Assessment Program (ITAP) for Hepatitis B Virus Surface Antigen (HBsAg) Point-of-Care (POC)* Diagnostics. Available at https://www.cimit.org/radx-tech-itap-for-hepatitis-b-virus-surface-antigen. Accessed October 18, 2024.
(8) Avellon A, Ala A, Diaz A, et al. Clinical performance of Determine HBsAg 2 rapid test for Hepatitis B detection. *J Med Virol*. 2020;92(12):3403-3411. doi:10.1002/jmv.25862
(9) Dembele B, Affi-Aboli R, Kabran M, Sevede D, Goha V, Adiko AC, Kouamé R, Allah-Kouadio E, Inwoley A. Evaluation of Four Rapid Tests for Detection of Hepatitis B Surface Antigen in Ivory Coast. J Immunol Res. 2020 Jun 26;2020:6315718. doi: 10.1155/2020/6315718.
(10) World Health Organization. WHO list of prequalified in vitro diagnostic products. Available at https://extranet.who.int/prequal/sites/default/files/document_files/list-of-prequalified-in-vitro-diagnostic-products_1.pdf. Accessed October 18, 2024.
(11) Jeng WJ, Lok AS. How to achieve a functional cure for chronic hepatitis B infection. *Clin Liver Dis (Hoboken)*. 2024;23(1):e0134. Published 2024 Apr 26. doi:10.1097/CLD.0000000000000134.
(12) Degasperi E, Anolli MP, Lampertico P. Towards a Functional Cure for Hepatitis B Virus: A 2022 Update on New Antiviral Strategies. *Viruses*. 2022;14(11):2404. Published 2022 Oct 29. doi:10.3390/v14112404.

(13) Yuen MF, Lim SG, Plesniak R, et al. Efficacy and Safety of Bepirovirsen in Chronic Hepatitis B Infection. *N Engl J Med*. 2022;387(21):1957-1968. doi:10.1056/NEJMoa2210027.